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| EXAMINER | |
|---|---|
| SLOBODYANSKY, ELIZABETH | |
| ART UNIT | PAPER NUMBER |
| 1652 | |

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/889,609 | SNYDER ET AL. | |
| | Examiner | Art Unit | |
| | Elizabeth Slobodyansky, PhD | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *39-97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *40-46,51 and 53-57* is/are allowed.

6)☒ Claim(s) *52,59 and 67-97* is/are rejected.

7)☒ Claim(s) *39,47-50,58-66* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The amendment filed December 29, 2003 and duplicated December 30, 2003 replacing the abstract, canceling claims 1-38 and adding claims 39-97 has been entered.

Claims 39-97 are pending.

### *Priority*

It is noted that human sequences set forth in SEQ ID NOs: 9 and 10 are first disclosed in the prior provisional application 60/144,839 filed July 21, 1999.

Mouse sequences set forth in SEQ ID NOs: 1 and 8 are first disclosed in the prior provisional application 60/116,333 filed January 19, 1999.

### *Claim Objections*

Claims 39, 47-50 and 58-66 are objected to because of the following:

The claims recite "mammalian serine racemase" while referring to either "human serine racemase" or "mouse serine racemase". Referring to "human" or "mouse" serine racemase is preferred.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 67-97 are rejected under 35 USC §112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 67-76 are drawn to or depend from a mammalian serine racemase having at least 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO:8 or SEQ ID NO:10 and a specific activity of at least 0.075 μmole L-serine/mg/hour. Claims 77-85 are drawn to or depend from polynucleotides encoding said racemases. Claims 86-97 are drawn to or depend from polynucleotides having at least 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO:1 or SEQ ID NO:9 and encoding mammalian serine racemases having a specific activity of at least 0.003μmole L-serine/mg/hour.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent

said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification the genus of mammalian serine racemases is represented by a single mouse serine racemase of SEQ ID NO:8 that is encoded by SEQ ID NO:1 and a single human serine racemase of SEQ ID NO: 10 that is encoded by SEQ ID NO:9. Those sequences that are "mammalian" are a subset of this genus of polypeptides having at least 85% amino acid sequence identity to SEQ ID NO:8 or SEQ ID NO:10 and having a specific racemase activity or a subset of the genus of serine racemases encoded by polynucleotides at least 85% identical to SEQ ID NO:1 or SEQ ID NO: 9. In this case, the specification fails to define those structural features of SEQ ID NO:8 or SEQ ID NO:10 that are commonly possessed by members of the genus that distinguish them from other "non-mammalian" polypeptides. Similarly, the specification fails to define those structural features of SEQ ID NO:1 or SEQ ID NO: 9 that are commonly possessed by members of the genus that distinguish them from other polynucleotides encoding "non-mammalian" polynucleotides. Thus, one skilled in the art cannot visualize or recognize the identity of the members of the genus. Furthermore, the specification fails to describe the identifying characteristics present within the genus of mammalian serine racemases that impart the specific requisite activity. As such, the two representative species do not adequately describe this

subset according to its structure so that one of skill in the art can visualize and distinguish those amino acid or nucleotide sequences that are mammalian, particularly in view of the larger genus that includes both mammalian and non-mammalian sequences. Therefore, the instant claims are not adequately described.

Claims 67-97 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for serine racemase of SEQ ID NOs: 8 or 10 and polynucleotides encoding thereof, including SEQ ID NOs: 1 or 9, does not reasonably provide enablement for mammalian serine racemase having an amino acid sequence 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NOs: 8 or 10 and a specific defined activity, a polynucleotide encoding thereof or a polynucleotide 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NOs: 1 or 9 and encoding a mammalian racemase having a specific defined activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, how to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification does not support the broad scope of the claims which encompass any mammalian serine racemase having at least 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO:8 or SEQ ID NO:10 and a specific activity of at least 0.075 μmole L-serine/mg/hour, polynucleotides encoding thereof and polynucleotides having at least 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO:1 or SEQ ID NO:9 and encoding mammalian serine racemases having a specific activity of at least 0.003μmole L-serine/mg/hour for the following reasons.

The specification does not teach mammalian species other than human, mouse and rat having homologous racemases. Furthermore, the specification does not teach and the current state of the art does not allow to predict which of mammalian species that have a specific percent identity to the sequences of the instant invention will have a specific requisite racemase activity. While the claims recite different specific racemase activities, the specification does not teach which of mammalian species produce racemases with a requisite activity. It is unknown which residues are responsible for changing activity from 0.003 μmole L-serine/mg/hour to 5 μmole L-serine/mg/hour.

While recombinant and assay techniques are known, it is not routine in the art to screen multiple organisms, as encompassed by the instant claims, with a reasonable expectation of success in obtaining the desired activity are limited in any protein and the result of such screening is unpredictable.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance,

beyond that provided, determination of mammalian serine racemases and genes encoding thereof as currently claimed is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 52 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 52 is incomplete as dependent from canceled claim 10.

Claim 59 is confusing as dependent from claim 56 where it appears it should depend from claim 58.

### *Allowable Subject Matter*

Claims 40-46, 51 and 53-57 are allowed.

### *Response to Arguments*

Applicant's arguments filed December 29, 2003 have been fully considered but they are not persuasive.

With regard to the 112, 1st paragraph, written description, Applicants argue that "Each of the species within the genus of racemases recited in claims 67-76 and 83-85 has common structural features. Each of the recited serine racemases has the common

structural feature of comprising an amino acid sequence that is at least 85% identical to either SEQ IDNO:8 or SEQ ID NO:10, where percent identity is determined using a specifically recited algorithm (Smith-Waterman) with particular, recited parameters (using an affine gap search with gap open penalty of 12, gap extension penalty of 1).

The sequence properties are a structural feature. Each of the serine racemases within the recited genus also has the functional property of having a specific activity of at least 0.075 μmole L-serine/mg/hour. The specification discloses such serine racemases on page 5, lines 21-23" (Remarks, page 15). Applicants apply similar considerations to polynucleotides (Remarks, page 16). Applicants' arguments are not found persuasive because the arguments are not related to a subgenus of mammalian serine racemases and polynucleotides encoding thereof. The claims of the instant application are limited to a genus of mammalian racemases and polynucleotides encoding thereof and the specification fails to convey the common structural characteristics of the single disclosed species of SEQ ID NO:8 such that one can visualize the members of the genus and distinguish a subgenus of "mouse" racemase having greater than 85% identity from the broader genus of racemases having greater than 85% identity. The specification fails to convey the common structural characteristics of the single disclosed species of SEQ ID NO:10 such that one can visualize the members of the genus and distinguish a subgenus of "human" racemase having greater than 85% identity from the broader genus of racemases having greater than 85% identity. Finally, the specification fails to convey the common structural characteristics of SEQ ID NO:8 or SEQ ID NO:10 such that one can visualize the

members of the genus and distinguish a subgenus of "mammalian" racemase having greater than 85% identity from the broader genus of racemases having greater than 85% identity. As such, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

With regard to the 112, 1st paragraph, enablement rejection, Applicants argue that "The Office Action also asserts that the specification does not enable a serine racemase having an amino acid sequence 85% identical to SEQ ID N0S:8 or 10 or encoded by a polynucleotide 85% identical to SEQ ID NOS:1 or 9. Office Action at page 5, second full paragraph. First, the U.S. Patent and Trademark Office's concern that the skilled artisan would not be able to chose which amino acids to substitute does not apply to serine racemases isolated from mammals other than mouse or human. Such racemases can naturally contain amino acid substitutions with respect to SEQ ID NOS:8 or 10. The specification teaches how to isolate such serine racemases: Mammalian serine racemase can be isolated from homogenates of mammalian brain, such as rat, mouse, or preferably human brain" (page 17). It is agreed that a highly homologous gene is enabled. However, there is no teaching as to which of the numerous mammalian species has the specific defined requisite activity that is within the claimed range.

Applicants further argue that "The specification discloses the Smith-Waterman algorithm recited in claims 66-97 and used to determine percent identity with

the disclosed sequences. See page 7, lines 7-11, and page 11, lines 29-32. Claims 66-97 also recite the particular parameters to be used in the algorithm: the percent identity is determined according to the Smith-Waterman homology search algorithm, using an affne gap search with gap open penalty of 12 and a gap extension penalty of 1." See claims 66 and 86. The Smith-Waterman homology search algorithm was published in 1981, well before the January 19, 1999 priority date of the present application. Smith & Waterman, "Identification of Common Molecular Subsequences,"J Mol Biol. 1981 Mar 25;147(1):195-7. Thus, on the application's priority date, those of skill in the art were familiar with using the algorithm to identify proteins having amino acid or polynucleotide sequences at least 85% identical to a reference sequence" (pages 18-19).

There is no dispute that the Smith-Waterman and other algorithms and methods of altering a protein sequence and methods of screening for racemase activity were well known in the art at the time of the invention. However, neither the specification nor the prior art provides the necessary guidance for altering the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:10 with an expectation of success for maintaining racemase activity. Such alteration(s) is/are HIGHLY unpredictable. Applicants further argue that "the specification teaches that mouse and human serine racemases contain a pyridoxal 5' phosphate binding region (ELFQKTGSFKIRGA). See page 5, lines 30-31, SEQ ID NO:8 (amino acids 47-60, and SEQ ID NO:10 (amino acids 47-60). Because this binding region is conserved between the mouse and human serine racemases, one skilled in the art would realize its importance and be wary of making changes in this region" (page 20). While it is correct that the specification teaches pyridoxal

5' phosphate binding region, the claims have no limitation for an amino acid sequence to comprise said region. Applicants argue that "If making amino acid substitutions in SEQ ID NOS:8 or 10, for example, one skilled in the art would tend to substitute amino acids with similar properties (*i.e.*, to make conservative amino acid substitutions). The universe of amino acids that can be substituted conservatively is well defined in the art (*e.g.*., Val-Ile-Leu, Asp-Glu, Lys-Arg, Asn-Gln, and Phe-Trp). See Alberts et al., eds., MOLECULAR BIOLOGY OF THE CELL, 1983, pages 58-59 (attached)" (page 20). This is not persuasive because the claims are not limited to conservative substitutions and because there is no guidance as to at which positions conservative substitutions can be made without affecting the function.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

March 15, 2004